UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION **This Document Relates to All Actions**	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge

DECLARATION OF MICHAEL BOTTORFF, Pharm.D., FCCP, FNLA, CLS

I, Michael Bottorff, submit the following declaration to respond to the critiques set forth in plaintiffs' motion to exclude my opinions. This declaration is based upon well-founded medical and scientific principles and my scientific experience.

1. My academic and professional background are addressed in Section 1 of my revised expert report served on August 2, 2021, which is adopted and incorporated in its entirety.

2. In order to conduct research, write published manuscripts, give national/international presentations and teach to pharmacy, medicine and nursing students, I rely on the retrieval, analysis and synthesis of the medical and scientific literature.

3. I used this same process to review the medical and scientific literature on the relevant issues in this litigation. This, combined with my 40 years' experience conducting such processes, forms the basis for my opinions.

4. Specifically, I have independently conducted a literature review and research on the relevant issues in this litigation, including the metabolic fate, metabolism, and distribution of NDMA/NDEA and valsartan.

Understanding the Human Metabolic Systems that Process NDMA and NDEA is Essential to Analyzing any Potential for Human Carcinogenicity.

5. Plaintiffs state that I "did not consider literature that evidenced low doses of NDMA orally ingested by humans getting into the systemic bloodstream." (Motion at 14.)

6. When valsartan containing the trace levels of NDMA and NDEA detected in finished dose tablets is consumed, the NDMA and NDEA is metabolized separately from the valsartan API. Following absorption, the valsartan is independently metabolized leaving a sufficient amount to be released from the liver into the general circulation to deliver its desired pharmacological effect. The level of valsartan released into systemic circulation is measurable as an area under the serum concentration vs time curve (AUC) and is the key measurement for determining bioequivalence of a generic drug with the RLD. The NDMA or NDEA, after absorption, follows its own independent metabolic pathway in the liver where it is metabolized by "First-Pass Metabolism."

7. The liver is the first metabolizing organ system which NDMA and/or NDEA in the orally ingested valsartan will reach. As the body's natural detoxifier, the liver acts on the NDMA and NDEA to metabolize and excrete it in a process known as "First-Pass Metabolism." Notably, the studies evaluating the capacity of the liver to metabolize NDMA demonstrate that there is a level below which there was either no mutations or cancers,[1] or only mutations and no cancer detected in downstream organs,[2] thereby confirming a "threshold level" below which there is no evidence of increased risk of cancer.

[1] Gomez M. I. D. et al., The Absorption and Metabolism in Rats of Small Oral Doses of Dimethylnitrosamine, Biochem. J. 164:497-500 (1977).
[2] Peto R, Gray R, Brantom P, Grasso P, Effects on 4080 rats of chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine: a detailed dose-response study. Cancer Res. 51(23 Pt 2):6415-51. PMID: 1933906 (1991) ("Peto 1991a").

8. NDMA has no potential carcinogenic effect unless it is metabolized, which is primarily by a specific cytochrome enzyme known as CYP4502E1.[3] Once metabolized, the resulting compound is highly reactive and will quickly bind with neighboring cells and will not escape the liver. According to the EPA document referenced by plaintiffs concerning body-scaling, the document explains why I did not apply body-weight scaling (adjustment between species for weight differences) to my analysis, and instead used a direct mg/kg comparison between humans and rats. The EPA document states: "[The] applicability of $BW^{3/4}$ scaling is less well **supported when toxicity is a consequence of exposure to a very reactive parent compound or metabolite** that is not removed from the site of formation by biological processes (e.g., subsequent metabolism) but chemically reacts with cellular constituents." (citation omitted). This is clearly the case for NDMA and NDEA in the liver after First-Pass Metabolism.

9. It is my opinion to a reasonable degree of scientific certainty that based upon the capacity of the liver to completely metabolize the trace levels of NDMA and NDEA in the affected valsartan tablets, that virtually none of the NDMA and NDEA contained in daily doses of valsartan will reach the systemic circulation (beyond the liver), much less any of the downstream organs, i.e. organs which are physiologically sequential to the liver after an orally administered compound.

Calculations Should be Performed Based on the Levels Actually Detected in Valsartan Medication and Normal Sized Adult Patients, not High Doses in Rodent Studies.

10. Plaintiffs argue that I erred in scaling to 70 kg rather than 50 kg body weight for humans.

11. My opinions were based on my analysis of the highest-dose valsartan tablets tested by FDA and the midpoint of the corresponding levels of NDMA and NDEA reportedly detected. I applied my analysis to a 70 kg patient which is considered a "normal sized adult" patient. Based

[3] NDEA likewise is metabolized by cytochrome P450 enzymes known as 2E1 and 2A6.

on my personal knowledge and understanding, 70 kg is commonly used as the weight of a normal adult when calculating doses of pharmaceutical drugs or evaluation of a chemical exposure on a "normal adult." I have also calculated the results for a 50 kg adult with the same outcome and again demonstrated the levels of NDMA and NDEA in valsartan were hundreds of times lower than the non-carcinogenic doses in the animal studies.

12. It should be noted that FDA did not calculate a "dose formula" as plaintiffs assert but rather it was an "acceptable daily intake" (ADI) based on rat carcinogenicity data and an ultra-conservative level of risk equating to 1 case of cancer in 100,000 persons taking the ADI for 70 years.[4] This assumes a linear dose-response relationship at even the lowest exposures without a threshold dose for a carcinogenic response.

13. The doses of NDMA and NDEA given to laboratory animals in the studies I have reviewed and relied upon are measured in mg/kg of body weight and given for the lifetime of the animal. I identified and analyzed dose-response studies, with cancer as an endpoint, where multiple doses were given where the study, by design, identified a dose below which no carcinogenicity was observed.[5] I extrapolated these non-carcinogenic doses mg/kg doses on a one-to-one basis to determine what that non-carcinogenic dose would be in a 70 kg human and found it to be hundreds, sometimes thousands, of times higher than the highest NDMA and NDEA exposure in the affected valsartan. In fact, the EPA document, to which plaintiffs refer in their

[4] The rodent data for the TD50 is measured in mg/kg, and FDA accepted these figures without performing the "interspecies scaling" plaintiffs suggest should have been applied for my calculations.

[5] *See, e.g.*, Peto R, Gray R, Brantom P, Grasso P, Effects on 4080 rats of chronic ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine: a detailed dose-response study. Cancer Res. 51(23 Pt 2):6415-51. PMID: 1933906 (1991); Ito N et al., Induction of preneoplastic and neoplastic lesions in rats treated N-nitroso compounds, IARC Sci Publ. (41):597-601 (1982).; Brantom P G, Dose-Response Relationships in Nitrosamine Carcinogenesis, The British Industrial Biological Research Association (BIBRA) (1983).

criticism of my use of the 70 kg patient, itself uses 70 kg for its toxicological assessment when extrapolating mgs/kg doses from animal studies.[6]

14. This methodology reliably calculates and analyzes the risk, if any, of exposure to humans of the same compound in the same dose per kg. There is no distinction in the methodology applied when calculating dose-conversions based upon whether the compound is carcinogenic or non-carcinogenic – the conversion is the same. In fact, some experts recommend to only use mg/kg conversion without any scaling for carcinogenicity studies.[7]

15. The doses of NDMA and NDEA given to animals to determine the TD50 level (a dose where tumors develop in 50% of the rodents) are measured in mg/kg without scaling. FDA applied the exposure levels for the TD50 reported in mg/kg from *Peto* and other studies in the FDA's AI calculation – notably without making any adjustment for "body weight scaling" to humans in the manner plaintiffs contend is appropriate. Notably, even applying the "body weight scaling" method described in the EPA document referenced in plaintiffs' papers when converting the *Peto* study doses of NDMA and NDEA to humans, the results would still be hundreds of times higher than the NDMA and NDEA exposure in the affected valsartan.

16. The World Health Organization (Table 2, 2002)[8] estimated that NDMA ingestion in adults from water and food to be an upper limit of 0.012 mcg/kg/day. In a 70kg adult (they use 71 and 72 kg in adults 20-59 years and 60 years and above respectively), this amounts to a total

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[6] "The mg/kg value is then derived by applying the human weight to this exposure, 96.25 mg/ 70 kg (human body weight), to arrive at the 1.4 mg/kg scaled human intake." Appendix B, Recommended Use of Body Weight3/4 as the Default Method in Derivation of the Oral Reference Dose, EPA/100/R11/0001

[7] Monro A, Mordenti J. Expression of exposure in negative carcinogenicity studies: dose/body weight, dose/body surface area, or plasma concentrations? Toxicol Pathol. 1995 Mar-Apr;23(2):187-98. doi: 10.1177/019262339502300213. PMID: 7569674.

[8] Liteplo, RG, et al. (WHO), Concise International Chemical Assessment Document 38: N-nitrosodimethylamine, IPCS Concise International Chemical Assessment Documents (2002).

daily exogenous exposure of 0.84 mcg, or only about 4% of the amount of NDMA ingested in valsartan products. Therefore, studies that detect NDMA in blood or urine after a meal are measuring *in vivo*/endogenous production of NDMA from precursors, i.e. nitrites/nitrates, found in the same foods that contain pre-formed NDMA. Dietary nitrites, for instance, are ingested at amounts almost 9000x higher than NDMA.[9] Accordingly, it is not scientifically sound to suggest that the presence of NDMA outside the liver following food ingestion means that NDMA escaped the first pass capacity of the liver. The article by Dr. Fine does not make this conclusion.

17. My analysis which determined there was no risk of cancer from the level of exposure detected in the affected valsartan tablets is based on the levels of NDMA and NDEA reported in animal studies as being a non-carcinogenic dose, and using principles of first-pass metabolism to explain why this would be the case. The trace levels of NDMA and NDEA in the affected valsartan tablets are well below any of the doses, i.e., exposure levels, in any animal study where NDMA or NDEA reportedly caused cancer. It is not material to this analysis to try and determine whether there might be some level of NDMA or NDEA, far above what is relevant in this litigation, that could cause cancer in humans, as the focus of my report was to scientifically explain why and how the lack of cancer at certain exposure levels could be explained by basic principles of pharmacokinetics and first pass metabolism.

Literature Search and Review Methodology.

18. Plaintiffs challenge my literature review as incomplete and "biased." (Motion at 13.)

19. My literature search included all animal studies on NDMA and/or NDEA from

[9] Jakszyn P, Bingham S, Pera G et al, *Endogenous versus exogenous exposure to N-nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study*, Carcinogenesis 27:1497-1501 (2006).

which I then analyzed and selected those that reported on multiple doses, such as *Peto* 1991a. I then analyzed those studies to determine the doses at which the study reported NOEL (No Observed Effect Level) or there was no carcinogenicity reported. My methodology included studies where NDMA or NDEA was shown to cause cancer in lab animals at certain doses, as well as demonstrating certain dose where no cancer was reported. There are consistent findings across the animal studies with sufficient dose data that low levels of NDMA and/or NDEA did not cause cancer which clearly show there is a 'threshold' below which there is no risk of cancer.

I declare under penalty of perjury that the foregoing is true and correct.

MICHAEL BOTTORFF, Pharm.D., FCCP, FNLA

Signature

2/24/2022

Date